Overview

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Title: AZD1480, a Phase I Study of a Novel JAK2 Inhibitor in Solid Tumors

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Author Summary: Abstract and Brief Discussion

Background

AZD1480 is a novel agent that inhibits Janus-Associated Kinases 1 and 2 (JAK-1/2). The primary objective of this Phase 1 study was to investigate the safety and tolerability of AZD1480 when administered as monotherapy to patients with solid tumors.

Methods

Thirty-eight patients with advanced malignancies were treated at doses from 10–70 mg QD and 20–45 mg BID.

Results

Pharmacokinetic analysis revealed rapid absorption and elimination with minimal accumulation after repeated QD or BID dosing. Exposure increased in a dose-dependent manner from 10–50 mg. Cmax was attained ~1 hr post-dose and T1/2 was ~5 hr. Pharmacodynamic analysis of circulating granulocytes demonstrated maximum pSTAT3 inhibition 1–2 hours post dose, coincident with Cmax, and greater pSTAT3 inhibition at higher doses. The average pSTAT3 inhibition in granulocytes at the highest dose tested, 70 mg QD, was 56% (standard deviation ± 21%) at steady state drug levels. Dose limiting toxicities (DLTs) consisted of pleiotropic neurologic adverse events, including dizziness, anxiety, ataxia, memory loss, hallucinations, and behavior changes. These were generally reversible with dose reduction or treatment cessation.

Conclusions

Whether the DLTs were due to inhibition of JAK-1/2 or off-target effects is unknown. The unusual DLTs and lack of clinical activity led to discontinuation of development.

Discussion

Constitutive activity of the JAK/STAT signaling pathway has been implicated in a wide range of solid tumors including prostate, head and neck, glioblastoma, colorectal and ovarian cancers [1–6]. AZD1480 is a novel JAK-1/2 inhibitor, shown to suppress growth of solid tumor xenografts [7]. In this phase I study, AZD1480 was administered as an oral continuously dosed daily (QD) or twice daily (BID) monotherapy to patients with advanced solid tumors at eight dose levels ranging from 10–70 mg QD, and 20–45 mg BID using a standard 3+3 design. AZD1480 had fast absorption, fast elimination, and dose dependent increase in exposure from 10–50 mg. One patient, treated at 30 mg BID, submitted pre- and post-treatment tumor biopsies, analysis of which showed a 50% reduction in phosphorylated STAT3, indicating pharmacodynamic effect. There were no RECIST responses. One patient with lung cancer had stable disease for greater than four months (145 days). There were no dose limiting toxicities (DLTs) noted at any of the QD doses. Based on PK analysis, twice daily dosing cohorts were subsequently opened. DLTs were noted at three of the four BID dose levels. All DLTs were neuropsychiatric in nature (dizziness, ataxia, hallucinations and anxiety) and were reversible in all but one case of grade 3 anxiety. Inclusive of the DLTs, neuropsychiatric adverse events of any grade were reported by 53% of patients in the BID dosing cohorts, with dizziness and ataxia being the most common. The mechanism of this unusual toxicity profile is unclear. One hypothesis is that off target inhibition of TRKB caused the wide range of neuropsychiatric effects observed in this trial, based on data showing that AZD1480 is equipotent against the TRK family (TRKA, TRKB, TRKC). TRKB is a receptor tyrosine kinase with signaling activated by nurotrophins [8]. Anxious behavior has been demonstrated in mice with inactivated TRKB [9]. An alternate hypothesis is that the CNS penetration of AZD1480 affected JAK signaling in the brain. In Rats, AZD1480 had good Blood Brain Barrier penetration with Brain:Blood ratio of 0.5. At this time there are insufficient data to differentiate between these hypotheses. Unfortunately, this unusual toxicity profile and overall lack of clinical activity led to discontinuation of development of AZD 1480. JAK2 targeting remains an area of active investigation in solid tumors.

Trial Information

Disease:	Advanced cancer/Solid Tumor Only
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	No designated number of regimens
Type of study - 1:	Phase I
Type of study - 2:	Other
Primary Endpoint:	Tolerability
Secondary Endpoint:	Maximum Tolerated Dose
Additional Details of Endpoints or Study Design:	
Investigator's Assessment of Activity:	Pharmacodynamic Endpoints Met

Drug Information

Drug 1:

Generic/Working name:	AZD1480
Trade name:	
Company name:	Astra Zeneca
Drug type::	Small molecule
Drug class:	JAK kinase
Dose:	milligrams (mg) per flat dose
Route:	oral (po)
Schedule of Administration:	Daily and Twice Daily

Dose Level	Dose of Drug: AZD1480	Number Enrolled	Number of Evaluable for Toxicity
1	10 mg QD	4	3
2	20 mg QD	3	3
3	40 mg QD	4	4
4	70 mg QD	6	6
5	20 mg BID	6	5
6	30 mg BID	7	5
7	35 mg BID	5	3
8	45 mg BID	3	2

Patient Characteristics

Number of patients, male:	14
Number of patients, female:	24
Stage:	IV
Age:	Median (range): 54 (31–74)
Number of prior systemic therapies:	Median (range): Not Collected
Performance Status: ECOG:	Not Collected
Other:	Patients were required to be ECOG Performance Status 0, 1 or 2.
Cancer Types or Histologic Subtypes	

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	73
Number of patients enrolled:	38
Number of patients evaluable for toxicity:	38
Number of patients evaluated for efficacy:	32
Evaluation method:	
Response assessment CR:	0%
Response assessment PR:	0%
Response assessment SD:	37%
Response assessment PD:	47%
Response assessment other:	16%
(Median) duration assessments PFS:	n/a
(Median) duration assessments TTP:	n/a
(Median) duration assessments OS:	n/a
(Median) duration assessments response duration:	n/a
(Median) duration assessments duration of treatment:	n/a

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades

*No Change from Baseline/No Adverse Event

Adverse Events Legend

Serious Adverse Events

Name	Grade	Attribution
Psychiatric Disorders/Anxiety	3	Possible

Dose Level	Dose of Drug: AZD1480	Number Enrolled	Number of Evaluable for Toxicity	Number with a Dose Limiting Toxicity	Dose Limiting Toxicity Information
1	10 mg QD	4	3	0	
2	20 mg QD	3	3	0	
3	40 mg QD	4	4	0	
4	70 mg QD	6	6	0	
5	20 mg BID	6	5	1	Ataxia/Grade 2
6	30 mg BID	7	5	1	Dizziness/Grade 3
7	35 mg BID	5	3	2	Hallucination/Grade 2 Anxiety/Grade 2
8	45 mg BID	3	2	0	

Pharmacokinetics/Pharmacodynamics

Dose Level	Number Enrolled	Cmax (μg/L) mean ± SD	T_{max}(h) (min - max)	AUC_{0-12} (h*12μg/L) mean ± SD	T ½(h) mean ± SD	Cl F (L/h) mean ± SD	Dose of Drug
1	4	229 ± 22.4	0.5 – 4.0	738 ± 420	4.06 ± 0.228	14.8 ± 8.19	10 mg QD
2	3	775 ± 260	0.75 – 1.0	1840 ± 683	5.59 ± 3.28	10.2 ± 3.90	20 mg QD
3	4	1410 ± 452	0.50 – 1.0	5110 ± 1040	4.78 ± 0.371	7.33 ± 0.831	40 mg QD
4	6	1050 ± 457	0.75 – 4.0	4170 ± 2960	9.34 ± 5.45	21.6 ± 11.7	70 mg QD
5	6	560 ± 281	0.76 – 1.9	1440 ± 911			20 mg BID
6	7	558 ± 205	0.5 – 2.1	1880 ± 1864			30 mg BID
7	5	783 ± 430	0.5 – 1.0	1930 ± 1240			35 mg BID
8	3	1557 ± 740	0.98 – 1.0	4684 ± 3881			45 mg BID

Assessment, Analysis, and Discussion

Completion:	Study terminated before completion
Completed Study Assessment:	Pharmacodynamic Endpoints Met
Investigator's analysis:	Drug Less Tolerable Than Expected

Discussion

Constitutive activity of the JAK/STAT signaling pathway has been implicated in a wide range of solid tumors including prostate, head and neck, glioblastoma, colorectal and ovarian cancers [1–6]. AZD1480 is a novel JAK-1/2 inhibitor, shown to suppress growth of solid tumor xenografts [7]. In this phase I study, AZD1480 was administered as an oral continuously dosed daily (QD) or twice daily (BID) monotherapy to patients with advanced solid tumors at eight dose levels ranging from 10–70 mg QD, and 20–45 mg BID using a standard 3+3 design. AZD1480 had fast absorption, fast elimination, and dose dependent increase in exposure from 10–50 mg. One patient, treated at 30 mg BID, submitted pre- and post-treatment tumor biopsies, analysis of which showed a 50% reduction in phosphorylated STAT3, indicating pharmacodynamic effect. There were no RECIST responses. One patient with lung cancer had stable disease for greater than four months (145 days). There were no dose limiting toxicities (DLTs) noted at any of the QD doses. Based on PK analysis, twice daily dosing cohorts were subsequently opened. DLTs were noted at three of the four BID dose levels. All DLTs were neuropsychiatric in nature (dizziness, ataxia, hallucinations and anxiety) and were reversible in all but one case of grade 3 anxiety. Inclusive of the DLTs, neuropsychiatric adverse events of any grade were reported by 53% of patients in the BID dosing cohorts, with dizziness and ataxia being the most common. The mechanism of this unusual toxicity profile is unclear. One hypothesis is that off target inhibition of TRKB caused the wide range of neuropsychiatric effects observed in this trial, based on data showing that AZD1480 is equipotent against the TRK family (TRKA, TRKB, TRKC) in enzyme assays. TRKB is a receptor tyrosine kinase with signaling activated by nurotrophins [8]. Anxious behavior has been demonstrated in mice with inactivated TRKB [9]. However there is a ten-fold drop-off in cell-based potency against TRKA and cell-based activity against TRKB has not been evaluated. An alternate hypothesis is that the CNS penetration of AZD1480 affected JAK signaling in the brain. In Rats, AZD1480 had good Blood Brain Barrier penetration with Brain: Blood ratio of 0.5. At this time there are insufficient data to differentiate between these hypotheses. Unfortunately, this unusual toxicity profile and overall lack of clinical activity led to discontinuation of development of AZD 1480. JAK2 targeting remains an area of active investigation in solid tumors.

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Figure and Table

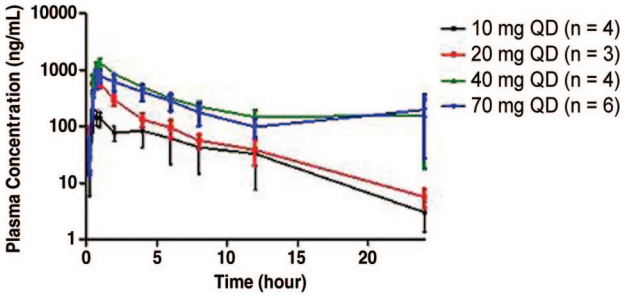

Figure 1 — Plasma Concentration (mean ± SD) of AZD1208 vs. Profile on Day 1.

Table 1. Dose escalation and dose limiting toxicities

Dose level	Dose of drug	Number enrolled	Number evaluable for toxicity	Number with a dose limiting toxicity	Dose limiting toxicity information
1	10 mg QD	4	3	0	
2	20 mg QD	3	3	0	
3	40 mg QD	4	4	0	
4	70 mg QD	6	6	0	
5	20 mg BID	6	5	1	Ataxia/grade 2
6	30 mg BID	7	5	1	Dizziness/grade 3
7	35 mg BID	5	3	2	Hallucination/grade 2 Anxiety/grade 3
8	45 mg BID	3	2	0	

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